Osteoporosis Clinical Trial Design: Regulatory History

Osteoporosis Drug Development
FDA Public Workshop
November 4, 2015

Stephen Voss M.D.
Division of Bone, Reproductive and Urologic Products
Center for Drug Evaluation and Research
Osteoporosis Guidance 1994

- Preclinical studies: “no detrimental effect on bone quality (including bone histology, density and strength)” in 2 species
- Clinical data:
  - Normal bone quality (biopsy) in a subset of pts at 3 yr
  - BMD ↑ “statistically and clinically significant”
  - Positive trend (p<0.2) in 3-year fracture data, with “no deterioration in the third year”
  - Fracture study must continue (post-marketing) to “5 years or as needed to show fracture reduction”
Phase 3 clinical trial design

• ≥ 3-year, randomized, double blind
• Placebo or active control
• Primary endpoint: new morphometric vertebral fx
• Other efficacy endpoints:
  – clinical fractures (each major type and combined all types)
  – BMD
  – bone turnover markers
Treatment of PMO phase 3 trials since 1994 Guidance

- Placebo-controlled, 3 years (except teriparatide)
- Primary endpoint: lumbar spine BMD (supportive fx data)
  - Alendronate (approved 1995), FIT ongoing
- Primary endpoint: new morphometric vertebral fx
  - Raloxifene (approved 1999)
  - Risedronate (2000)
  - Teriparatide (2002)
  - Ibandronate (2003)
  - Zoledronic acid (2007)
  - Denosumab (2010)
Trial duration
# Trial Duration: Etidronate

<table>
<thead>
<tr>
<th></th>
<th>Lumbar spine BMD</th>
<th></th>
<th>New vertebral fractures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change from baseline</td>
<td></td>
<td>% of subjects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>Year 3</td>
<td>Year 0 → 2</td>
<td>Year 2 → 3</td>
</tr>
<tr>
<td>Etidronate</td>
<td>4.9</td>
<td>5.1</td>
<td>6.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.5</td>
<td>1.0</td>
<td>12.1</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Am J Med 1993; 95:557
PMO fracture trials:
Vertebral fracture efficacy by year

<table>
<thead>
<tr>
<th></th>
<th>Absolute Risk Reduction (%) vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year (cumulative)</strong></td>
<td><strong>Year 1</strong></td>
</tr>
<tr>
<td>Etidronate</td>
<td>-</td>
</tr>
<tr>
<td>Alendronate (FIT-1)</td>
<td>-</td>
</tr>
<tr>
<td>Risedronate (VERT-NA)</td>
<td>4.0</td>
</tr>
<tr>
<td>Risedronate (VERT-MN)</td>
<td>7.7</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>0.6*</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>2.2</td>
</tr>
<tr>
<td>Denosumab</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*NS. Sources: Prescribing information (RIS, ZOL, DEN); Lancet 1996, 348:1535 (ALN); JBMR 2004, 19:1241 (IBD); Am. J. Med. 1993, 95: 557 (ETID)
PMO fracture trials: Vertebral fracture efficacy by year

<table>
<thead>
<tr>
<th>Year (cumulative)</th>
<th>Relative Risk Reduction (% vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>Etidronate</td>
<td></td>
</tr>
<tr>
<td>Alendronate (FIT-1)</td>
<td></td>
</tr>
<tr>
<td>Risedronate (VERT-NA)</td>
<td>65</td>
</tr>
<tr>
<td>Risedronate (VERT-MN)</td>
<td>61</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>58*</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>60</td>
</tr>
<tr>
<td>Denosumab</td>
<td>61</td>
</tr>
</tbody>
</table>

## PMO fracture trials:
### Non-vertebral fracture efficacy by year

<table>
<thead>
<tr>
<th>Year (cumulative)</th>
<th>Relative Risk Reduction (% vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>Alendronate (FIT-1/2)</td>
<td>15</td>
</tr>
<tr>
<td>Risedronate (VERT-NA)</td>
<td>41</td>
</tr>
<tr>
<td>Risedronate (VERT-MN)</td>
<td>15</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>16</td>
</tr>
<tr>
<td>Denosumab</td>
<td>16</td>
</tr>
</tbody>
</table>

Trial Duration

- Current approach: vertebral fracture efficacy can be demonstrated in 2 years for most drugs
- Longer periods may be needed to evaluate hip fractures, depending on sample size
- A trial duration of 2 or 3 years will not adequately address questions regarding potential long term safety concerns
Active control trials
Are placebo-controlled osteoporosis trials still appropriate?

• Declaration of Helsinki 2002: placebo unethical if effective therapy exists and use of placebo may lead to serious or irreversible harm

• FDA AC meeting 2002: Placebo-controlled trials are still appropriate/ feasible in many circumstances
  – Many women with PMO don’t receive/ cannot tolerate existing treatments
  – All trial participants receive calcium/vitamin D supplements
  – Discontinuation option for subjects with new fracture or bone loss
Placebo-controlled osteoporosis trials: Lower-risk study populations

• Exclude women with multiple/severe/recent vertebral fx or hip fx
• Relative risk reductions are similar between high-risk and moderate-risk pts (e.g. FIT-1 and FIT-2)
  – fracture data can be extrapolated across risk groups
• Larger trials
• Powered for nonvertebral and hip fractures
• > 90% outside U.S.
Active-control trials

- Superiority or non-inferiority (NI)
- If NI: must be adequate background documentation of the reproducible efficacy of the active control in the study population
- Active-test difference greater than a “clinically significant threshold” should be ruled out by confidence interval analysis
- 1994 Guidance: no recommendations on the choice of active control or the NI margin
Active Control BMD Trials

• BMD generally acceptable as primary endpoint for supplemental trials of approved drugs with fracture efficacy; BTMs supportive
  • New formulations or dosing regimens
  • BMD non-inferiority at 1 year
    – NI margins based on maintaining a prespecified fraction of the treatment effect of the original regimen/formulation
• BMD alone is not acceptable for comparative efficacy claims (either superiority or NI) between two approved drugs; fracture data is needed
Active-control fracture trials

- Appropriate for high-risk or moderate-risk pts
- Superiority:
  - anabolic vs. antiresorptive
- Non-inferiority:
  - drugs in same class
Active-control fracture trials: Non-inferiority

• Very large sample sizes needed
  – probably feasible for vertebral fractures
  – not feasible for hip fractures

• Assay sensitivity uncertain
  – placebo-controlled fx data (e.g. in moderate-risk pts) may be preferred over non-inferiority fx data (e.g. in high-risk pts)
  – potential advantages of a new drug (e.g. safety, convenience) should also be considered
Thank you